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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/402,093	OHSUYE ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Elizabeth Slobodyansky, PhD	1652	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 March 2004.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 27,29-40,45 and 47-53 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 27, 29-40, 45, 47-53 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

The amendment filed March 29, 2004 canceling claims 1, 6-11, 13, 14, 16-23, 25, 26, 41-44 and 46, amending claims 27, 29, 34, 38-40, 45, 48 and 49 and adding claims 50-53 has been entered.

Claims 27, 29-40, 45 and 47-53 are pending.

### ***Specification***

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: throughout the specification the terms "RHHGP[G]" and "RHHGP-1" have been assigned SEQ ID NO:25 by the amendment filed December 26, 2002. For example, the specification recites "Figure 16 is [ ] of RHHGP[G] [SEQ ID NO: 25]" (page 8, beginning at line 12); "Figure 17 is [ ] of RHHGP[G] [SEQUENCE ID NO:25] to RHHGP-1 [SEQUENCE ID NO:25]" (page 8, beginning at line 14, emphasis added); "a fusion protein ... referred to hereinafter as RHHGP[G]" (e.g., page 21, lines 5-13); "amidated GLP-1(7-36)NH<sub>2</sub> (referred to hereinafter as RHHGP-1) [SEQ ID NO:25]" (page 23) (see also at least pages 24, 30, 33).

Furthermore, the use of brackets in" [SEQ ID NO:25]" introduced by the amendment (instead of parentheses) is confusing because brackets may indicate the deleted terms.

Appropriate correction is required.

It is noted that in the Sequence Listing filed June 7, 2002, SEQ ID NO:25 is given as "Arg His His Gly Pro Xaa", where Xaa=Gly instead of given as "Arg His His Gly Pro Gly". Further, the sequences of SEQ ID NO: 25 and SEQ ID NO: 8 both are described as "amino acid sequence containing a site cleaved by Kex2 Protease" wherein neither sequence appears to contain said site.

### ***Claim Objections***

Claims 27, 29-40, 45 and 47-53 are objected to because of the following:

The claims have been amended to recite "the peptide of interest – helper peptide unit" (emphasis added). The term "unit" is not present in the specification. It is suggested that the claims are reworded to recite "a fusion protein comprising from the N-terminal to the C-terminal a protective peptide, a helper peptide and a peptide of interest", for example.

Claims 38-40, 45, 50 and 51 have been amended to delete the abbreviation "GLP-1". Because the abbreviation "GLP-1" is used throughout the specification, it is suggested that the first time that the abbreviated term is written out in full it is followed by its abbreviation in parenthesis.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 29-40, 45 and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 27, 29-40, 45 and 47-53 are drawn to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide that is added to the peptide of interest - helper peptide unit, a vector and a cell comprising thereof.

Claims 27, 29-37, 47-49, 52 and 53 do not limit a peptide of interest by either structure or function. Therefore, the claims recite a genus of peptides of interest, a genus of helper peptides and a genus of protective peptides. These genera encompass an infinite number of peptides of any structure and from any source both naturally occurring and man made as long as the isoelectric point of the fusion protein is between 8-12. Claims 38-40, 45, 50 and 51 are directed to a peptide of interest, GLP-1 derivative.

The specification defines GLP-1 derivatives as following: "in addition to the above-mentioned GLP-1 (7-37) and GLP-1(7-36) NH<sub>2</sub>, there can be mentioned peptides having an insulintropic activity in which amino acid residues have been substituted for, added to, and/or deleted from the peptide comprising 37 amino acid residues of GLP-1, peptides having an insulintropic activity in which amino acids of said peptide have been further modified (for example, an amidated form), and peptides having an insulintropic activity that are obtained from the combinations thereof" (paragraph bridging pages 11-12, emphasis added). Since the number of allowed substitutions, additions and/or depletions is not limited, the GLP-1 derivative can have the amino acid sequence with an unknown homology to human GLP-1.

Thus, the genus of DNAs that comprise the DNA molecules encoding GLP-1 and derivatives thereof is a large variable genus with the potentiality of encoding GLP-1 peptides from different natural sources such as hamster and human, for example, and many different man made derivative peptides. Therefore, many structurally and functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a three species of the claimed genus of fusion proteins comprising human GLP-1 (Figures 11-13). The specification does not disclose the isoelectric points of said fusion proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of encoding a GLP-1 derivative and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other

peptide of interest. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of the species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 27, 29-40, 45 and 47-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making derivatives of human GLP-1 using fusion proteins shown at Figures 7, 11-13 (SEQ ID NOs: 20-23) or said fusion proteins wherein a given GLP-1 derivative is substituted by any of GLP-1 derivatives recited in the specification (pages 12-13), does not reasonably provide enablement for a process of making a peptide of any structure and/or function or GLP-1 derivative using other helper and protective peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 27, 29-40, 45 and 47-53 are directed to a method for producing a highly purified peptide. Therefore, they are drawn to a method of making of a genus of a polypeptide of an unknown function and having any characteristics as long as the isoelectric point of the fusion protein is between 8 and 12. While the specification teaches a method of making of a highly purified GLP-1 derivative, it does not provide any guidance as to a process for producing a highly purified peptide of any function and characteristics. This would involve designing a helper peptide-peptide of interest fusion

with the only limitation of having isoelectric point in the wide range of 8-12. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find the helper peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use the fusion of protective peptide, helper peptide and peptide of interest in a claimed method.

The state of the art is such that it is unpredictable which helper should be used for each peptide of interest, to enable the claimed method for any peptide of interest, and the specification provides no guidance on the matter. With regard to claims 38-40, 45, 50 and 51, the specification provides no guidance as to what are other helper peptides that can be used instead of the ones present in SEQ ID NOs: 19-23.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted *a priori*. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an appropriate

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purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

### ***Response to Arguments***

Applicant's arguments filed March 29, 2004 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, written description rejection "Applicants respectfully assert that recitation of the structure of GLP-1 is not necessary, as this peptide is well known" (Remarks, pages 12-13). While the structure of human GLP-1 is known (e.g., Bell et al.), the term "GLP-1" encompasses the peptide from any source, i.e. a peptide of an unknown structure. Further, the claims are drawn to a GLP-1 derivative, i.e. a peptide that may have low or no structural homology to human GLP-1. The rejection is over a written description of a genus of GLP-1 derivatives having an unknown amino acid sequence.

With regard to the 112, 1st paragraph, enablement rejection, "Applicants respectfully assert that undue experimentation is not necessary to arrive at the subject matter claimed in Claims 27, 29-40, 45, and 47-49. As admitted by the Examiner, the Specification enables a process for making GLP-I using fusion proteins shown at Figures 1 1-13 and for making a highly purified GLP-I . See Official Action mailed

September 29, 2003, Pages 7-9. Applicants assert that those skilled in the art could readily call upon their skill and the information contained in the Specification to expand upon the recited principles to make and use the subject matter claimed in Claims 27, 29-40, 45, and 47-49" (pages 13-14). This is not persuasive for the reasons explained above in the rejection. It is necessary for one of ordinary skill in the art to know or be provided with guidance for the selection of which of the infinite number of protective peptide, helper peptide, peptide of interest have the requisite ability to ultimately produce a purified peptide of interest. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As such the amount of experimentation required to make and use the currently claimed scope is still deemed to be undue.

The 102, 103 and 112, 2<sup>nd</sup> paragraph rejections are moot in view of the amendment.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Elizabeth Slobodyansky, PhD  
Primary Examiner  
Art Unit 1652

June 24, 2004